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MEMO

TO: All Field Personnel with Responsibility for VIOXX

FROM: Market Integration Team for VIOXX

SUBJECT: Top Ten Obstacle Handlers

Enclosed is the complete Obstacle Handling Guide for VIOXX. This Guide includes all obstacle responses issued since the launch of VIOXX. Though it is important for you to be familiar with all of the obstacle handlers, the following Top Ten Obstacle Handlers are the most important obstacle handlers at this time as they center around current issues in the field.

Cardiovascular Events

Obstacle Response #7- "Can VIOXX be used in patients using low dose aspirin?"

Obstacle Response #23- "I am concerned about the cardiovascular effects of VIOXX."

Obstacle Response #38- "The competition has been in my office telling me that the incidence of heart attacks (or cardiovascular events) is greater with VIOXX than Celebrex." OR "I just read (or heard) a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

Renal Effects

Obstacle Response #4- "I am concerned about the potential edema that occurs with VIOXX."

Obstacle Response #20- "Can I use VIOXX with Ace Inhibitors?"

Obstacle Response #31- "I am concerned about dose-related increases in hypertension with VIOXX."

VIOXX 50mg Tablet

Obstacle Responses #9 and 9a- "Why wasn't VIOXX 50mg studied for longer than five days in acute pain?" OR "VIOXX cannot be used for longer than five days when treating patients for acute pain."

Obstacle Response #30- "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

General

Obstacle Response #26- "I use Celebrex. I'm concerned about the safety profile of VIOXX."

Obstacle Response #34- "I understand the new COX-2 agent, MOBIC, was just approved."

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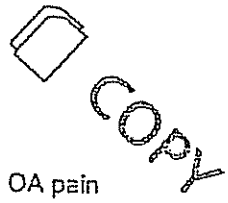
JAN 30 2006

RUSTY NICHOLS, CLERK
Marengo County, Alabama



23. "I am concerned about the cardiovascular effects of VIOXX."

24. "Your PI states that VIOXX provided a significant reduction in OA pain after one to two weeks. Why should I use VIOXX when Celebrex states OA patients achieved significant reduction in pain within 24-48 hours after initiation of dosing?"

25 "Do I have to discontinue VIOXX pre or post-operatively?"

26. "I use Celebrex. I'm concerned about the safety profile of VIOXX. (Cumulative vs. Additive clarification)

27. "Why are you telling me not to prescribe Celebrex for sulfa-allergic patients when Hyzaar has the same contraindication?"

28. "The two recent JAMA articles showed that Celebrex provided greater reductions in events than VIOXX." OR "It looks like there are still a lot of PUB's in the VIOXX group; why is the reduction only 50% and not 100%?"

29. "I understand Celebrex just received an FDA approval for prevention of cancer. Is VIOXX receiving a similar indication soon?"

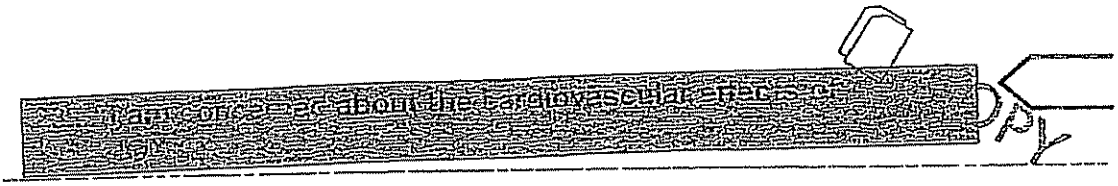
30. "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

31. "I am concerned with dose-related increases in hypertension with VIOXX."

32. "Celebrex must be a safer agent Unlike VIOXX, Celebrex outcomes data did not show any increases in myocardial infarctions or stroke."

33. "Why didn't VIOXX report the p-values for its' OUTCOMES STUDY?" DELETED

34 "I understand the new COX-2 agent, Mobic, was just approved."



Clarify:
What is your specific concern?

The physician may respond:
(A) "I am hesitant to use VIOXX in my patients because it may worsen CHF," or
(B) "VIOXX has the potential to increase the risk of MI."

Response to (A) "I am hesitant to use VIOXX in my patients because it may worsen CHF."
Doctor, as you know, there are precautions you should take when prescribing any NSAID for your patients with CHF. Because once daily VIOXX® is an NSAID, you should consider taking these same precautions when considering the use of once daily VIOXX® for this specific patient population.

Clinical trials with once daily VIOXX® 12.5 mg and 25 mg have shown renal effects such as hypertension and lower extremity edema similar to those observed with comparator NSAIDs. VIOXX® should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or edema.

(NOTE: If the physician asks about concomitant use with ACEIs, refer to Obstacle Response No. 20.)

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

Response to (B) "VIOXX increases the risk of MI."

Doctor, once daily VIOXX has no effect on platelet aggregation, and therefore would not be expected to demonstrate reductions in MI or other CV events. Agents such as low-dose aspirin are routinely prescribed for CV patients for their effect on the inhibition of platelet aggregation. Therefore, once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis. However, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

(Refer to Obstacle Response No. 7.)

If probed further:
Offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
~~VIOXX PI ⇒ Precautions ⇒ Aspirin (V41)~~

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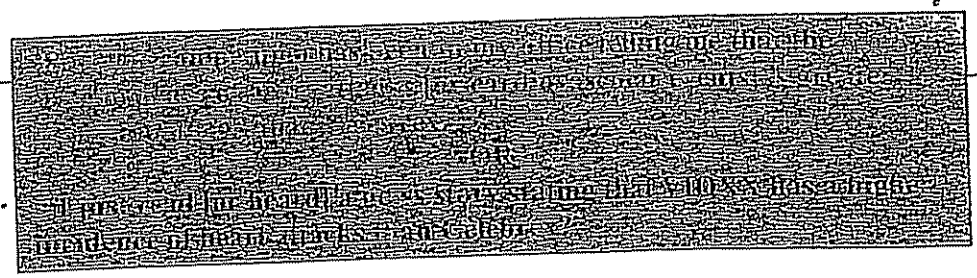

Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.4% with VIOXX and 0.1% with naproxen. Upon further analysis, four percent of patients in the VIOXX GI Outcomes Study had experienced a cardiac event such as a heart attack or stroke before entering the study and thus met the established criteria for the use of aspirin for secondary CV prophylaxis. In the remaining 96% of patients for whom aspirin was not indicated for secondary CV prophylaxis, the incidence of MI was lower—0.2% for VIOXX and 0.1% for naproxen. This difference was not statistically significant.

In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0 3% with diclofenac, and 0.5% with ibuprofen. They also presented data for patients who were not prescribed aspirin. In this group, the incidence of MI was 0.2% for Celebrex and 0.1% for the comparator NSAIDs Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX

NOTE: There will be an additional PIR to address these issues available shortly.

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them,

In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.